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Cancer Following Irradiation in Childhood and Adolescence

John D. Boice, Jr., ScD

INTRODUCTION

This paper provides an overview of what is known concerning the oncogenic effects of radiation exposure during childhood and adolescence. The study populations include atomic bomb survivors, patients given radiotherapy to treat cancer or benign diseases, patients who received rather massive exposures during diagnostic radiographic procedures, persons exposed to environmental radiation, and children who received occupational exposures when working in underground mines (Table I).

ATOMIC BOMB SURVIVORS

Studies of survivors of the atomic bombs dropped on Hiroshima and Nagasaki in 1945 have provided valuable information on cancer risks following radiation exposure [1]. The increase in recorded deaths due to either leukemia or solid tumors following exposures between 0.5 and 1 Gy are both statistically significant. The dose-response relationship for leukemia appears linear quadratic with a suggestion of a leveling off of risk at the highest doses. For radiation-induced solid tumors, the dose-response curve appears consistent with a straight line. There also is a suggestion at the highest doses that there might be a plateauing of effect, possibly related to the dominance of cell-killing over transformation at very high doses. A recent major publication on cancer incidence included articles clearly defining the oncogenic risks of radiation for many sites [2,3]. Cancer types with the highest relative risk coefficients include leukemia, breast, thyroid, and lung cancer. The particular mix of tumors following relatively low-dose whole-body exposures to the atomic bombs is different from that following therapeutic exposures in childhood, when sarcomas, brain tumors, and several other sites appear more often. It is also clear that children are at higher relative risk of radiation-induced cancers than adults (Table II). For practically all sites the relative risk at 1 Gy is greater for those under the age of 20 at exposure than those over the age of 20. This age difference is particularly notable for leukemia, thyroid, breast, and skin cancer. Lung cancer is the only site for which the relative risk is elevated more among adults than children. On the other hand, the absolute excess risk is generally higher among adults than children (Table II), reflecting the much higher natural incidence of cancer at these older ages.

Recent studies of radiogenic breast cancer clearly show the modifying effect that age at exposure can have [4]. The highest breast cancer risk in atomic bomb survivors occurs among children under the age of ten in 1945, and risk then decreases with increasing age at exposure. In fact, for women exposed after the menopausal ages, the radiation risk is low and on the borderline of detectability. A recent analysis has suggested that radiation may have interacted with an underlying genetic susceptibility to enhance the occurrence of breast cancer at a very early age, under the age of 35 [5]. Another provocative finding from the atomic bomb survivors is the indication that the adult thyroid gland is relatively immune to the carcinogenic action of radiation. There was no significant excess of thyroid cancer linked to radiation if exposure occurred after the age of 20. Further, for all forms of leukemia taken together, it appeared that the latent interval, that is the time between exposure and the occurrence of clinical disease, was inversely related to the age at exposure. Children under the age of 15 at the time of the bombings developed leukemia within a relatively short time whereas adults took many more years before radiogenic leukemia occurred. After the minimal latency, a wavelike pattern of risk over time was suggested with risk then decreasing, but not to normal levels, among the long-term survivors.

RADIOTHERAPY FOR CANCER

There are a number of quantitative studies that have enhanced our understanding of late effects following radiotherapy in childhood. It is clear that second cancers developed at a very high rate. In an early study conducted by the Late Effects Study Group (LESG), approximately 12% of 2-year survivors develop a second malignancy

From the National Cancer Institute, Radiation Epidemiology Branch, Bethesda, Maryland

Address reprint requests to John D. Boice, Jr., Sc.D., Chief, Radiation Epidemiology Branch, National Cancer Institute/NIH, Executive Plaza North, Rm. 408, Bethesda, MD 20892.

TABLE I. Studies of Children and Adolescents Exposed to Radiation

Atomic bomb survivors
Radiotherapy for cancer
Retinoblastoma
Bone, thyroid, leukemia
Acute leukemia
Hodgkin's disease
Radiotherapy for benign disease
Thymus
Tinea capitis
Tonsils
Ra-224 for bone disease
Diagnostic radiography
Tuberculosis
Scoliosis
Environmental/occupation
Nuclear installations
Radon
Chernobyl

TABLE II. Radiation Risk Estimates by Age at Exposure, A-Bomb Incidence, 1994

	RR at 1 Gy		Excess risk[a]	
Cancer	<20 yr	≥20 yr	<20 yr	≥20 yr
Esophagus	4.32	1.13	0.41	0.24
Stomach	1.74	1.24	2.87	6.15
Colon	1.62	1.70	0.48	2.71
Liver	2.39	1.19	1.78	0.95
Bladder	1.71	1.79	0.20	1.62
Lung	1.57	2.06	0.41	8.27
Skin	6.37	1.39	1.04	0.58
Breast	4.32	1.98	10.29	4.36
Thyroid	8.89	1.10	3.84	0.10
Leukemia	7.11	4.70	2.28	3.06
All solid cancers	2.40	1.46	NA	NA

[a]Excess cancers per 10,000 persons per year per Gy. NA denotes data not available.

after 25 years from their initial diagnoses [6]. Such global estimates of risk among childhood cancer survivors, however, will differ depending upon the particular mix of primary tumors evaluated as well as differences in therapeutic practices.

The first study to attempt to quantify the risk of leukemia by estimated radiation dose to active bone marrow was negative [7]. The cumulative risk for developing leukemia within the entire cohort at 25 years was 0.8% among all 9,170 children, whereas it was 4.2% among the 1,036 children treated for Hodgkin's disease. However, in a nested case-control study, there was no evidence that radiotherapy increased the risk of leukemia in this study. One possible interpretation is that the very high doses to localized areas of the bone marrow were so large that the critical cells were killed or rendered incapable of division and that this process overcame that associated with cellular transformation. Subsequent studies in the United Kingdom have suggested a radiotherapy risk in combination with other childhood cancer treatments such as alklyating agents and epipodophyllotoxins [8]. The excess leukemia seen in the earlier LESG study was explained in large part by high-dose chemical treatments which carried a substantial risk of leukemia.

Radiation-induced thyroid disease was also evaluated in the same LESG series, [9]. There was clear evidence of an increasing risk with an increasing amount of radiation dose to the thyroid, over 60 Gy. However, the risk at these very high levels, although 12-fold, was much less than would be predicted based on whole-body exposures in childhood among the atomic bomb survivors. Again, this suggests the possible effects of cellular killing in modifying the radiation dose-response relationship. Radiation-induced bone cancer was also evaluated in this LESG early cohort [10]. Overall, at approximately 25 years of follow-up, 5.5% of the survivors developed a bone tumor in the entire cohort, whereas 14.1% of the survivors of retinoblastoma, for whom a genetic susceptibility for osteosarcoma is known, developed a bone tumor. Of note is the fact that a radiation dose response was observed for both retinoblastoma patients and children with other diseases. This is the first evidence of a dose–response relationship in any study for radiation-induced bone cancer following external radiation. There was no risk seen following exposures under 10 Gy but risk increased to over 20-fold following exposures over 40 Gy. Interestingly, the pattern of risk for retinoblastoma and other childhood cancers was similar, suggesting that radiation was interacting in a multiplicative fashion with genetic and other factors that might be related to subsequent bone cancer risk.

The risk of second cancers has been evaluated recently in a large study of patients with retinoblastoma treated in New York and Massachusetts [11]. Over 1,600 patients were evaluated, including 919 with bilateral or germline disease. The risk of death due to second malignancies was exceptionally high: 89 occurred against three expected, with the preponderance of excess deaths being due to osteosarcoma, soft tissue sarcoma, skin melanomas, and brain tumors. The relative risk decreased with increasing years of follow-up, but the absolute risk (excess risks per person per years of follow-up) increased dramatically. These findings underline the need for further follow-up as these children reach the ages in later life when cancer occurrence is high. Females had a higher risk than males for developing a second tumor, an observation that was also made among radiogenic cancers seen in the atomic bomb survivors. Further, children exposed under the age of one were at much higher risk than those exposed at later ages. The cumulative risk approached 30% at 40 years for children with hereditary disease,

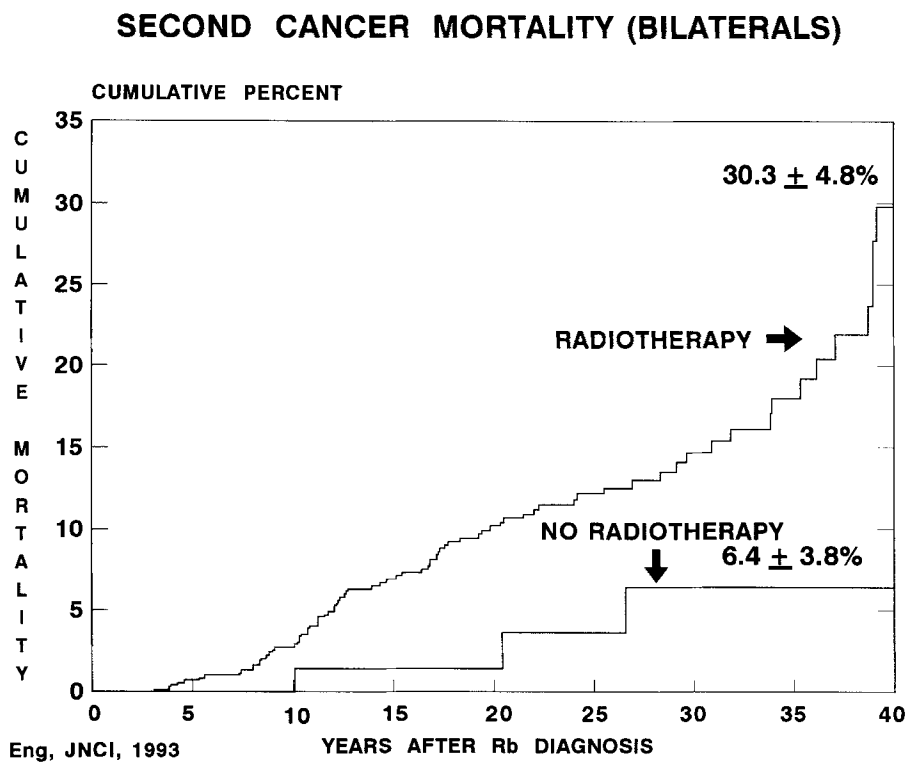

Fig. 1. Cumulative risk of death due to a second cancer among children with bilateral retinoblastoma treated with and without radiotherapy [11].

whereas those with unilateral or sporadic disease without a family history showed cumulative incidences that were similar to normal expectation. Among patients treated with radiotherapy for bilateral disease, there was strong evidence to suggest that radiotherapy interacted with the underlying genetic susceptibility to enhance the development of osteosarcomas in the facial area (Fig. 1).

For many years it has been known that meningiomas and brain tumors may occur following high dose cranial irradiation. An important study of 9,720 children treated for acute lymphocytic leukemia has carefully documented the excess of second tumors within the clinical trial setting. Significant excesses of brain cancers as well as lymphomas, leukemias and other tumors, including thyroid, were reported [12]. The risk was higher among the children who received irradiation and was also higher among the children who were under the age of 5 years when treated.

Given the success of treatments for childhood cancers, these patients are now living much longer and are at risk for late effects. In an important series from Stanford, the risk of radiation-induced breast cancer was evaluated following treatment for Hodgkin's disease. The doses to the breast were on the order of 40 Gy and a significant excess of breast cancer cases was seen: however, the excess only occurred among those under the age of 30 when treated and was highest among the children under the age of 20 [13]. This indicates, again, the high sensitivity of the children and adolescents to the induction of malignancies which become apparent much later in life.

RADIOTHERAPY FOR BENIGN DISEASE

There have been a number of important studies of children who were irradiated for benign diseases such as enlarged thymus glands, ringworm of the scalp, large tonsils [14], and benign bone disease. As early as 1918, it was recommended in the clinical literature that irradiation of the thymus gland should be considered for newborns. In studies of children with "thymic enlargement" who received radiotherapy, clear excesses of thyroid cancer have been reported with the relative risk reaching 60-fold following 8 Gy of radiation [15–17]. Interestingly, studies of radiation-induced breast cancer among children irradiated for enlarged thymus glands have also found excesses [18]. This indicates that the immature breast among children, even those under age one, can be affected by radiation and that many years later breast cancer can develop. It is interesting that the latent period for radiogenic breast cancer appears inversely related to age at exposure. The newborns did not develop excess breast cancers in their teenage years or in their twenties but in their forties and later life, that is, at those ages where the risk of cancer begins to increase in adults. It is somewhat

disquieting to appreciate that a single exposure in childhood can cause changes that remain latent for 30 or 40 years and then is expressed as the occurrence of a malignant tumor.

Children irradiated for ringworm of the scalp have provided important information on the risk of thyroid, brain, and skin cancers [19–22]. In a large series from Israel, thyroid cancer was significantly elevated following what appeared to be scatter radiation to the thyroid gland on the order of 0.1 Gy. The risk was also highest among the children treated who were under the age of 5 years. Death due to leukemia was elevated indicating that the cranial bone marrow was sufficiently exposed to result in radiation damage leading to leukemia. Later in life, children also lost their hair due to the very high doses that they received, particularly in areas where the exposure fields overlapped. Brain cancer also was found to be substantially elevated, not only meningiomas, but also gliomas and more aggressive tumors. Skin cancer was increased in the facial areas. Interestingly, the skin cancers occurred near the scalp line and not in the areas where the hair would grow over, suggesting the need for ultraviolet light to interact with the radiation damage to bring about the skin cancer. In one series in New York, it was clear that skin pigmentation was an important cofactor in that no skin cancers occurred among the black children who were treated and basal cell carcinomas occurred in excess only among whites [23].

A large pooling of all the major data sets of radiation-induced thyroid cancer made it clear that the childhood thyroid gland is very sensitive to the carcinogenic effects of radiation. However, when exposures occurred after the age of fifteen, there is very little evidence that radiation in fact results in a thyroid cancer increase. In a unique study at the Boston Children's Hospital, thyroid nodule disease was evaluated by two methods. One was based on responses to a mail questionnaire sent to those who had been irradiated for enlarged tonsils with doses to the thyroid gland of approximately 0.24 Gy. The relative risk by this method was high and on the order of 15-fold [24]. However, when the patients were called into the clinic for physical examination, the relative risk associated with enlarged tonsil treatment was much lower, or 2.7-fold. The reason for this difference was ascribed to an underascertainment of thyroid disease among the nonexposed surgical controls. It was postulated that the radiation alerts in the 1970s heightened the awareness of possible thyroid disease among the parents of children who had been exposed. Thus, they had received screening or evaluation to detect their nodular disease. On the other hand, those children who received surgical removal of their tonsils and adenoids were not so inclined to have any intense personal screenings, so there was a normal occurrence of nodular disease in this group. Thus, a radiation risk was identified based on clinical examinations, but it was not of the same magnitude as suggested in the questionnaire study. This indicates the importance that screening plays, with advancement in tumor occurrence due to early detection, when evaluating radiogenic thyroid cancers. A final interesting study showed that radium-224 used to treat bone disease in patients in Germany resulted in a substantial excess of bone sarcomas [25]. There was a suggestion that juveniles might be at higher risk than adults. Interestingly, no excess of leukemia was reported, likely related to the distribution of radium within the bone matrix not reaching the bone marrow cells of import for leukemia.

DIAGNOSTIC RADIOGRAPHY

Studies of tuberculosis patients treated with lung collapse in the 1930s and 1940s have clearly found breast cancer to be related to the many hundreds of chest fluoroscopies received during the monitoring of the lung collapse. In studies in Canada and Massachusetts, it was quite evident that age at exposure was an important determinant. The risk was concentrated among those exposed as adolescents, with only a very minimal or nondetectable risk among women over the age of 35 when exposed [26,27]. Despite the very high risks of breast cancer found in these series, it is interesting that no risk of lung cancer has been reported [28]. This suggests that tissues not only differ in their relative sensitivity to radiation, but they also differ with regard to the ability of fractionated exposures to cause demonstrable increases in cancer.

Another important study is that of young women with scoliosis. They underwent frequent x-ray screenings in the 1930s and 40s during their adolescent years to monitor curvature during the period of most rapid bone growth. An excess of breast cancer was found among these women [29]. The number of spinal x-ray films was quite large, over 40, with some young women receiving over 600. The dose to the breast was as high as 1.5 Gy. The excess of breast cancer reported was based on population rates; further study is needed to clarify the effect that nulliparity and other breast cancer risk factors might have played. It has been suggested that women heterozygous for ataxia-telangiectasia may be at high risk for radiation-induced breast cancer following diagnostic radiology [30], but the evidence is not very convincing [31].

ENVIRONMENTAL/OCCUPATIONAL EXPOSURES

There has been recent concern that preconception radiation during occupational exposures at a nuclear fuel reprocessing plant in the United Kingdom might be related to childhood cancer in the offspring [32]. These early concerns generated a tremendous amount of research in the United Kingdom and other countries which have not substantiated an increased risk [33]. A recent commentary

in *Nature* summarizes the current understanding of preconception irradiation and leukemia. It concludes that chance was the most likely reason for the apparent cluster around this particular facility [34]. It should be noted that studies of the atomic bomb survivors have not found any evidence of genetic effects among over 20,000 offspring [35]. Because of public concern, however, the National Cancer Institute conducted a comprehensive survey of the cancer risk in counties in the United States that contain nuclear reactors or DOE radiation facilities [36]. Overall, the study was negative and the risk for childhood leukemia was, in fact, higher before the nuclear reactors started than afterwards. These ecologic studies do not furnish definitive proofs, even though they provide some reassurance.

Radon is clearly a human carcinogen as seen in studies of underground miners [37]. There is evidence that exposures among children who began work under the age of 15, and even under the age of 10, caused high rates of lung cancer later in life. There did not appear to be any difference in the risk of lung cancer, however, with regard to age at exposure. Another interesting observation is that the excess relative risk per working level month, the unit of radon progeny exposure, was such that it decreased with years after exposure ceased. This implies that exposures to radon in the home during childhood are unlikely to be a major factor in the lung cancer burden because of the decrease in risk with follow-up time since exposure. Indeed, it appears difficult to link indoor radon exposure directly with convincing lung cancer risks in epidemiologic surveys [38].

The radiation reactor accident in Chernobyl in 1986 has, to date, not resulted in any detectable excesses of cancer in any of the population studied [39]. However, there has been a strong indication that thyroid cancer is excessive in children residing in Belarus at the time of the accident. They purportedly received high doses of radiation to the thyroid glands through the ingestion of radioiodines [40]. Over 200 thyroid carcinomas have occurred which is a remarkable increase in such a short calendar time. It is not clear at this time whether there is a causal relationship, however, because the latent period seems much too short for radiogenic thyroid cancers, there have been no evaluations to date with regard to estimated doses to the thyroid gland, and it remains peculiar that children in similarly exposed areas such as Russia have not shown this remarkable increase. One clinical study conducted in areas of high radiation deposition was negative, although the follow-up time might have been too short to detect a radiation excess [41]. One of the difficulties also in evaluating these results around Chernobyl has to do with the screening effect on the early detection of thyroid disease. It is clear in other studies of medically-exposed populations, that screening persons exposed in the past does result in a very large increase in the number of thyroid cancers detected. This increase occurs not only among those who received high doses but also among those receiving low doses [42]. Thus, it is not evident, at this time, how much of the increase in Belarus is related to the radiation received, observational bias due to early detection from screening, or other factors.

SUMMARY

The child appears more sensitive than the adult to the carcinogenic effects of radiation for certain sites such as the breast and thyroid. However, there are few studies of persons who were exposed as children and adolescents who have been followed for 40 or 50 years into the adult ages. Thus, it is extremely important that follow-up studies of children continue to evaluate the lifetime cancer risk that might be related to radiation exposures in childhood.

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